

Supplementary Appendix

Methods

Mutation screening

After obtaining informed consent from a patient's parents, DNA was isolated from a sample of whole blood or heart tissue. NGS of 182 cardiac disorder-related genes associated with cardiomyopathies and channelopathies (Table S1) was performed using an Ion PGM System (Life Technologies, Carlsbad, CA, USA).

This custom panel utilized two separate PCR primer pools, yielding a total of 1,870 amplicons and used to generate target amplicon libraries. Genomic DNA samples were PCR-amplified using the custom panel and an Ion AmpliSeq Library Kit v2.0 (Life Technologies, Carlsbad, CA, USA). Individual samples were labeled using an Ion Xpress Barcode Adapters Kit (Life Technologies) and then pooled at equimolar concentrations. Emulsion PCR and ion sphere particle (ISP) enrichment were performed using the Ion PGM Hi-Q OT2 Kit (Life Technologies), according to the manufacturer's instructions. ISPs were loaded onto a 316 chip and sequenced using an Ion PGM Hi-Q Sequencing Kit (Life Technologies).

Sanger sequencing

For all candidate pathogenic variants that passed these selection criteria, Sanger sequencing was used to validate the NGS results. For this, the nucleotide sequences of amplified fragments were analyzed by direct sequencing in both directions by using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) and sequence analysis was performed using an ABI 3130xl automated sequencer (Applied Biosystems).

Data analysis and variant classification

Torrent Suite and Ion Reporter Software 5.0 (Life Technologies) were used to perform primary, secondary, and tertiary analyses, including optimized signal processing, base calling, sequence alignment, and variant analysis.

The allelic frequency of all detected variants was determined using the Exome Aggregation Consortium (ExAC) database and Human Genetic Variation Database (HGVD), which contain data of 1,208 Japanese individuals. All variants with a minor allelic frequency of ≥ 0.005 in the ExAC and HGVD populations were excluded. To evaluate the pathogenicity of the remaining variants, we utilized seven different *in silico* predictive algorithms: FATHMM, SIFT, PROVEAN, Align GVGD, MutationTaster2, PolyPhen-2, and CADD (Table S2). Variants predicted to be deleterious or pathogenic by at least five of the seven *in silico* algorithms were considered likely pathogenic.

Table S1. List of 182 analyzed genes of NGS.

Gene	Chromosome	NCBI Reference Sequence:	Sequence : (Start..End)	
<i>ABCC9</i>	12p12.1	NG_012819.1	NC_000012.11 (21950323..22094797, complement)	http://www.ncbi.nlm.nih.gov/gene/10060
<i>ACAD9</i>	3q21.3	NG_017064.1	NC_000003.12 (128879490..128913114)	https://www.ncbi.nlm.nih.gov/gene/28976
<i>ACADVL</i>	17p13.1	NG_007975.1	NC_000017.11 (7217125..7225267)	https://www.ncbi.nlm.nih.gov/gene/37
<i>ACTC1</i>	15q14	NG_007553.1	NC_000015.9 (35080297..35087927, complement)	http://www.ncbi.nlm.nih.gov/gene/70
<i>ACTN2</i>	1q42-q43	NG_009081.1	NC_000001.10 (236849754..236927931)	http://www.ncbi.nlm.nih.gov/gene/88
<i>ADAMTS1</i>	21q21.3	NC_000021.9	NC_000021.9 (26836287..26845409, complement)	https://www.ncbi.nlm.nih.gov/gene/9510
<i>ADAMTS9</i>	3p14.1	NC_000003.12	NC_000003.12 (64515654..64688000, complement)	https://www.ncbi.nlm.nih.gov/gene/56999
<i>ADCK3</i>	1q42.13	NG_012825.2	NC_000001.11 (226939339..226987545)	https://www.ncbi.nlm.nih.gov/gene/56997
<i>AKAP9</i>	7q21-q22	NG_011623.1	NC_000007.13 (91570181..91739987)	http://www.ncbi.nlm.nih.gov/gene/10142
<i>AMPD1</i>	1p13.2	NG_008012.1	NC_000001.11 (114673098..114695618, complement)	https://www.ncbi.nlm.nih.gov/gene/270
<i>ANK2</i>	4q25-q27	NG_009006.2	NC_000004.11 (113739239..114304896)	http://www.ncbi.nlm.nih.gov/gene/287
<i>ARFGEF2</i>	20q13.13	NG_011490.1	NC_000020.11 (48921721..49036693)	https://www.ncbi.nlm.nih.gov/gene/10564
<i>BAG3</i>	10q25.2-q26.2	NG_016125.1	NC_000010.10 (121410859..121437331)	http://www.ncbi.nlm.nih.gov/gene/9531
<i>BMP10</i>	2p13.3	NG_032117.1	NC_000002.12 (68860916..68871517, complement)	https://www.ncbi.nlm.nih.gov/gene/27302
<i>BMPRIA</i>	10q22.3	NG_009362.1	NC_000010.10 (88516396..88684945)	http://www.ncbi.nlm.nih.gov/gene/657
<i>BOLA3</i>	2p13.1	NG_031910.1	NC_000002.12 (74135401..74147912, complement)	https://www.ncbi.nlm.nih.gov/gene/388962
<i>BRAF</i>	7q34	NG_007873.3	NC_000007.14 (140719327..140924928, complement)	https://www.ncbi.nlm.nih.gov/gene/673
<i>C10orf2</i>	10q24.31	NG_012624.1	NC_000010.11 (100987527..100994403)	https://www.ncbi.nlm.nih.gov/gene/56652
<i>CACNA1C</i>	12p13.3	NG_008801.2	NC_000012.11 (2079952..2807115)	http://www.ncbi.nlm.nih.gov/gene/775
<i>CACNA2D1</i>	7q21.11	NC_000007.14	NC_000007.14 (81946444..82443806, complement)	https://www.ncbi.nlm.nih.gov/gene/781
<i>CACNB2</i>	10p12	NG_016195.1	NC_000010.10 (18429373..18830688)	http://www.ncbi.nlm.nih.gov/gene/783
<i>CALR3</i>	19p13.11	NG_031959.2	NC_000019.9 (16589767..16607015, complement)	http://www.ncbi.nlm.nih.gov/gene/125972
<i>CAPN3</i>	15q15.1	NG_008660.1	NC_000015.9 (42646545..42704515)	http://www.ncbi.nlm.nih.gov/gene/825
<i>CASQ2</i>	1p13.1	NG_008802.1	NC_000001.11 (115700003..115768805, complement)	https://www.ncbi.nlm.nih.gov/gene/845
<i>CASZ1</i>	1p36.22	NC_000001.11	NC_000001.11 (10636604..10796676, complement)	https://www.ncbi.nlm.nih.gov/gene/54897

<i>CAV3</i>	3p25	NG_008797.2	NC_000003.11 (8775486..8788451)	http://www.ncbi.nlm.nih.gov/gene/859
<i>CDKN1C</i>	11p15.4	NG_008022.1	NC_000011.10 (2883218..2885804, complement)	https://www.ncbi.nlm.nih.gov/gene/1028
<i>COL4A1</i>	13q34	NG_011544.1	NC_000013.10 (110801310..110959496, complement)	http://www.ncbi.nlm.nih.gov/gene/1282
<i>COL7A1</i>	3p21.31	NG_007065.1	NC_000003.12 (48564073..48595302, complement)	https://www.ncbi.nlm.nih.gov/gene/1294
<i>CPT2</i>	1p32.3	NG_008035.1	NC_000001.11 (53196429..53214197)	https://www.ncbi.nlm.nih.gov/gene/1376
<i>CSRP3</i>	11p15.1	NG_011932.2	NC_000011.10 (19182030..19210571, complement)	https://www.ncbi.nlm.nih.gov/gene/8048
<i>CTNNA3</i>	10q21.3	NG_034072.1	NC_000010.11 (65912518..67696217, complement)	https://www.ncbi.nlm.nih.gov/gene/29119
<i>DAAMI1</i>	14q23.1	NG_047127.1	NC_000014.9 (59188657..59371405)	https://www.ncbi.nlm.nih.gov/gene/23002
<i>DAAM2</i>	6p21.2	NC_000006.12	NC_000006.12 (39792366..39904877)	https://www.ncbi.nlm.nih.gov/gene/23500
<i>DES</i>	2q35	NG_008043.1	NC_000002.11 (220283099..220291461)	http://www.ncbi.nlm.nih.gov/gene/1674
<i>DMD</i>	Xp21.2	NG_012232.1	NC_000023.10 (31137345..33357726, complement)	http://www.ncbi.nlm.nih.gov/gene/1756
<i>DMPK</i>	19q13.32	NG_009784.1	NC_000019.10 (45769709..45782557, complement)	https://www.ncbi.nlm.nih.gov/gene/1760
<i>DNAJC19</i>	3q26.33	NG_022933.1	NC_000003.12 (180983709..180989774, complement)	https://www.ncbi.nlm.nih.gov/gene/131118
<i>DSC2</i>	18q12.1	NG_008208.1	NC_000018.9 (28645938..28682388, complement)	http://www.ncbi.nlm.nih.gov/gene/1824
<i>DSG2</i>	18q12.1	NG_007072.3	NC_000018.9 (29078027..29128814)	http://www.ncbi.nlm.nih.gov/gene/1829
<i>DSP</i>	6p24	NG_008803.1	NC_000006.11 (7541808..7586946)	http://www.ncbi.nlm.nih.gov/gene/1832
<i>DTNA</i>	18q12.1	NG_009201.1	NC_000018.10 (34493290..34891844)	https://www.ncbi.nlm.nih.gov/gene/1837
<i>DVL1</i>	1p36.33	NG_008048.1	NC_000001.11 (1335278..1349142, complement)	https://www.ncbi.nlm.nih.gov/gene/1855
<i>EED</i>	11q14.2	NG_029595.1	NC_000011.10 (86244384..86285420)	https://www.ncbi.nlm.nih.gov/gene/8726
<i>ELN</i>	7q11.23	NG_009261.1	NC_000007.13 (73442119..73484237)	http://www.ncbi.nlm.nih.gov/gene/2006
<i>EMD</i>	Xq28	NG_008677.1	NC_000023.10 (153607597..153609883)	http://www.ncbi.nlm.nih.gov/gene/2010
<i>ERBB2</i>	17q12	NG_007503.1	NC_000017.11 (39688084..39728662)	https://www.ncbi.nlm.nih.gov/gene/2064
<i>ERBB4</i>	2q34	NG_011805.1	NC_000002.12 (211375717..212538628, complement)	https://www.ncbi.nlm.nih.gov/gene/2066
<i>EZH2</i>	7q36.1	NG_032043.1	NC_000007.14 (148807372..148884349, complement)	https://www.ncbi.nlm.nih.gov/gene/2146
<i>FBN2</i>	5q23.3	NG_008750.1	NC_000005.10 (128257909..128538042, complement)	https://www.ncbi.nlm.nih.gov/gene/2201
<i>FGF16</i>	Xq21.1	NG_034050.1	NC_000023.11 (77447675..77456522)	https://www.ncbi.nlm.nih.gov/gene/8823
<i>FGF9</i>	13q12.11	NG_016272.1	NC_000013.11 (21671076..21704501)	https://www.ncbi.nlm.nih.gov/gene/2254

<i>FGFR1</i>	8p11.23	NG_007729.1	NC_000008.11 (38411138..38468834, complement)	https://www.ncbi.nlm.nih.gov/gene/2260
<i>FGFR2</i>	10q26.13	NG_012449.2	NC_000010.11 (121478330..121598458, complement)	https://www.ncbi.nlm.nih.gov/gene/2263
<i>FKBP1A</i>	20p13	NC_000020.11	NC_000020.11 (1368977..1393172, complement)	https://www.ncbi.nlm.nih.gov/gene/2280
<i>FKBP1B</i>	2p23.3	NC_000002.12	NC_000002.12 (24033205..24067743)	https://www.ncbi.nlm.nih.gov/gene/2281
<i>FKTN</i>	9q31.2	NG_008754.1	NC_000009.12 (105558117..105655950)	https://www.ncbi.nlm.nih.gov/gene/2218
<i>FLNA</i>	Xq28	NG_011506.1	NC_000023.11 (154348532..154374638, complement)	https://www.ncbi.nlm.nih.gov/gene/2316
<i>FXN</i>	9q21.11	NG_008845.2	NC_000009.12 (69035563..69079077)	https://www.ncbi.nlm.nih.gov/gene/2395
<i>GAA</i>	17q25.2-q25.3	NG_009822.1	NC_000017.10 (78075339..78093680)	http://www.ncbi.nlm.nih.gov/gene/2548
<i>GATA4</i>	8p23.1-p22	NG_008177.1	NC_000008.10 (11534433..11617510)	http://www.ncbi.nlm.nih.gov/gene/2626
<i>GBE1</i>	3p12.2	NG_011810.1	NC_000003.12 (81489699..81761799, complement)	https://www.ncbi.nlm.nih.gov/gene/2632
<i>GFRA1</i>	10q25.3	NG_050620.1	NC_000010.11 (116056925..116273645, complement)	https://www.ncbi.nlm.nih.gov/gene/2674
<i>GFRA2</i>	8p21.3	NG_029215.1	NC_000008.11 (21690403..21789296, complement)	https://www.ncbi.nlm.nih.gov/gene/2675
<i>GLA</i>	Xq22	NG_007119.1	NC_000023.10 (100652779..100663001, complement)	http://www.ncbi.nlm.nih.gov/gene/2717
<i>GPD1L</i>	3p22.3	NG_023375.1	NC_000003.11 (32148003..32210207)	http://www.ncbi.nlm.nih.gov/gene/23171
<i>HADHA</i>	2p23.3	NG_007121.1	NC_000002.12 (26190635..26244726, complement)	https://www.ncbi.nlm.nih.gov/gene/3030
<i>HAS2</i>	8q24.13	NC_000008.11	NC_000008.11 (121613031..121641390, complement)	https://www.ncbi.nlm.nih.gov/gene/3037
<i>HBB</i>	11p15.4	NG_059281.1	NC_000011.10 (5225466..5227071, complement)	https://www.ncbi.nlm.nih.gov/gene/3043
<i>HCCS</i>	Xp22.2	NG_016460.1	NC_000023.11 (11111286..11123086)	https://www.ncbi.nlm.nih.gov/gene/3052
<i>HCN4</i>	15q24.1	NG_009063.1	NC_000015.9 (73612200..73661605, complement)	http://www.ncbi.nlm.nih.gov/gene/10021
<i>HEY2</i>	6q22.31	NC_000006.12	NC_000006.12 (125747639..125762243)	https://www.ncbi.nlm.nih.gov/gene/23493
<i>HMGCL</i>	1p36.11	NG_013061.1	NC_000001.11 (23801877..23825459, complement)	https://www.ncbi.nlm.nih.gov/gene/3155
<i>ITGA7</i>	12q13.2	NG_012343.1	NC_000012.12 (55684568..55716037, complement)	https://www.ncbi.nlm.nih.gov/gene/3679
<i>JARID2</i>	6p22.3	NC_000006.12	NC_000006.12 (15245975..15522042)	https://www.ncbi.nlm.nih.gov/gene/3720
<i>JUP</i>	17q21	NG_009090.2	NC_000017.10 (39910859..39942964, complement)	http://www.ncbi.nlm.nih.gov/gene/3728
<i>KCNE1</i>	21q22.12	NG_009091.1	NC_000021.8 (35790910..35884573, complement)	http://www.ncbi.nlm.nih.gov/gene/3753
<i>KCNE2</i>	21q22.12	NG_008804.1	NC_000021.8 (35736323..35743440)	http://www.ncbi.nlm.nih.gov/gene/9992
<i>KCNE3</i>	11q13.4	NG_011833.1	NC_000011.9 (74165886..74178600, complement)	http://www.ncbi.nlm.nih.gov/gene/10008

<i>KCNH2</i>	7q36.1	NG_008916.1	NC_000007.13 (150642044..150675402, complement)	http://www.ncbi.nlm.nih.gov/gene/3757
<i>KCNJ2</i>	17q24.3	NG_008798.1	NC_000017.10 (68164757..68176189)	http://www.ncbi.nlm.nih.gov/gene/3759
<i>KCNQ1</i>	11p15.5	NG_008935.1	NC_000011.9 (2466221..2870340)	http://www.ncbi.nlm.nih.gov/gene/3784
<i>KRAS</i>	12p12.1	NG_007524.1	NC_000012.11 (25358180..25403870, complement)	http://www.ncbi.nlm.nih.gov/gene/3845
<i>LAMP2</i>	Xq24	NG_007995.1	NC_000023.10 (119560003..119603204, complement)	http://www.ncbi.nlm.nih.gov/gene/3920
<i>LDB3</i>	10q22.3-q23.2	NG_008876.1	NC_000010.10 (88426542..88495829)	http://www.ncbi.nlm.nih.gov/gene/11155
<i>LMNA</i>	1q22	NG_008692.2	NC_000001.10 (156052369..156109880)	http://www.ncbi.nlm.nih.gov/gene/4000
<i>LMX1B</i>	9q33.3	NG_017039.1	NC_000009.12 (126614443..126701032)	https://www.ncbi.nlm.nih.gov/gene/4010
<i>LRPPRC</i>	2p21	NG_008247.1	NC_000002.12 (43886224..43996005, complement)	https://www.ncbi.nlm.nih.gov/gene/10128
<i>MADD</i>	11p11.2	NG_029462.1	NC_000011.10 (47269376..47330031)	https://www.ncbi.nlm.nih.gov/gene/8567
<i>MBL2</i>	10q21.1	NG_008196.1	NC_000010.11 (52764977..52772847, complement)	https://www.ncbi.nlm.nih.gov/gene/4153
<i>MED1</i>	17q12	NG_046996.1	NC_000017.11 (39404285..39451281, complement)	https://www.ncbi.nlm.nih.gov/gene/5469
<i>MEST</i>	7q32.2	NG_009226.1	NC_000007.14 (130486175..130506297)	https://www.ncbi.nlm.nih.gov/gene/4232
<i>MIB1</i>	18q11.2	NG_033272.2	NC_000018.10 (21740793..21870957)	https://www.ncbi.nlm.nih.gov/gene/57534
<i>MIPEP</i>	13q12.12	NG_052977.1	NC_000013.11 (23730189..23889448, complement)	https://www.ncbi.nlm.nih.gov/gene/4285
<i>MLYCD</i>	16q23.3	NG_009079.1	NC_000016.10 (83899125..83916182)	https://www.ncbi.nlm.nih.gov/gene/23417
<i>MMACHC</i>	1p34.1	NG_013378.1	NC_000001.11 (45500184..45511266)	https://www.ncbi.nlm.nih.gov/gene/25974
<i>MRPS22</i>	3q23	NG_012174.1	NC_000003.12 (139344014..139357129)	https://www.ncbi.nlm.nih.gov/gene/56945
<i>MTO1</i>	6q13	NG_032856.1	NC_000006.12 (73461731..73501456)	https://www.ncbi.nlm.nih.gov/gene/25821
<i>MYBPC3</i>	11p11.2	NG_007667.1	NC_000011.9 (47352957..47374253, complement)	http://www.ncbi.nlm.nih.gov/gene/4607
<i>MYCN</i>	2p24.3	NG_007457.1	NC_000002.12 (15940438..15947007)	https://www.ncbi.nlm.nih.gov/gene/4613
<i>MYH11</i>	16p13.11	NG_009299.1	NC_000016.9 (15796992..15950887, complement)	http://www.ncbi.nlm.nih.gov/gene/4629
<i>MYH6</i>	14q12	NG_023444.1	NC_000014.8 (23849942..23878836, complement)	http://www.ncbi.nlm.nih.gov/gene/4624
<i>MYH7</i>	14q12	NG_007884.1	NC_000014.8 (23881947..23904870, complement)	http://www.ncbi.nlm.nih.gov/gene/4625
<i>MYH7B</i>	20q11.22	NG_016984.2	NC_000020.11 (34955835..35002437)	https://www.ncbi.nlm.nih.gov/gene/57644
<i>MYL2</i>	12q24.11	NG_007554.1	NC_000012.11 (111348623..111358404, complement)	http://www.ncbi.nlm.nih.gov/gene/4633
<i>MYL3</i>	3p21.3-p21.2	NG_007555.2	NC_000003.11 (46899357..46904973, complement)	http://www.ncbi.nlm.nih.gov/gene/4634
<i>MYLK</i>	3q21	NG_029111.1	NC_000003.11 (123331143..123603149, complement)	http://www.ncbi.nlm.nih.gov/gene/4638

<i>MYOZ2</i>	4q26-q27	NG_029747.1	NC_000004.11 (120056939..120108944)	http://www.ncbi.nlm.nih.gov/gene/51778
<i>NEXN</i>	1p31.1	NG_016625.1	NC_000001.11 (77888515..77948643)	https://www.ncbi.nlm.nih.gov/gene/91624
<i>NFATC1</i>	18q23	NG_029226.1	NC_000018.10 (79395772..79529323)	https://www.ncbi.nlm.nih.gov/gene/4772
<i>NKX2-5</i>	5q34	NG_013340.1	NC_000005.9 (172659107..172662315, complement)	http://www.ncbi.nlm.nih.gov/gene/1482
<i>NNT</i>	5p12	NG_032869.1	NC_000005.10 (43601092..43705566)	https://www.ncbi.nlm.nih.gov/gene/23530
<i>NR0B1</i>	Xp21.2	NG_009814.1	NC_000023.11 (30304422..30309378, complement)	https://www.ncbi.nlm.nih.gov/gene/190
<i>NRAS</i>	1p13.2	NG_007572.1	NC_000001.10 (115247085..115259515, complement)	http://www.ncbi.nlm.nih.gov/gene/4893
<i>NRG1</i>	8p12	NG_012005.2	NC_000008.11 (31639222..32771716)	https://www.ncbi.nlm.nih.gov/gene/3084
<i>NSD1</i>	5q35.3	NG_009821.1	NC_000005.10 (177131835..177300213)	https://www.ncbi.nlm.nih.gov/gene/64324
<i>NUMB</i>	14q24.2-q24.3	NG_029061.2	NC_000014.9 (73275210..73458580, complement)	https://www.ncbi.nlm.nih.gov/gene/8650
<i>NUMBL</i>	19q13.2	NC_000019.10	NC_000019.10 (40665905..40690658, complement)	https://www.ncbi.nlm.nih.gov/gene/9253
<i>PKP2</i>	12p11	NG_009000.1	NC_000012.11 (32943680..33049780, complement)	http://www.ncbi.nlm.nih.gov/gene/5318
<i>PLEC</i>	8q24.3	NG_012492.1	NC_000008.11 (143915147..143976800, complement)	https://www.ncbi.nlm.nih.gov/gene/5339
<i>PLEKHM2</i>	1p36.21	NG_053033.1	NC_000001.11 (15681506..15734769)	https://www.ncbi.nlm.nih.gov/gene/23207
<i>PLN</i>	6q22.1	NG_009082.1	NC_000006.11 (118869442..118881587)	http://www.ncbi.nlm.nih.gov/gene/5350
<i>PMP22</i>	17p12	NG_007949.1	NC_000017.11 (15229777..15265373, complement)	https://www.ncbi.nlm.nih.gov/gene/5376
<i>POLG</i>	15q26.1	NG_008218.2	NC_000015.10 (89316305..89334795, complement)	https://www.ncbi.nlm.nih.gov/gene/5428
<i>PRDM16</i>	1p36.32	NG_029576.1	NC_000001.11 (3068227..3438621)	https://www.ncbi.nlm.nih.gov/gene/63976
<i>PRKAG2</i>	7q36.1	NG_007486.1	NC_000007.13 (151253200..151574316, complement)	http://www.ncbi.nlm.nih.gov/gene/51422
<i>PTGS2</i>	1q31.1	NG_028206.2	NC_000001.11 (186671812..186680427, complement)	https://www.ncbi.nlm.nih.gov/gene/5743
<i>PTK2</i>	8q24.3	NG_029467.1	NC_000008.11 (140658382..141002079, complement)	https://www.ncbi.nlm.nih.gov/gene/5747
<i>PTPN11</i>	12q24	NG_007459.1	NC_000012.11 (112856536..112947717)	http://www.ncbi.nlm.nih.gov/gene/5781
<i>RAD54L2</i>	3p21.2	NC_000003.12	NC_000003.12 (51538683..51668660)	https://www.ncbi.nlm.nih.gov/gene/23132
<i>RAF1</i>	3p25	NG_007467.1	NC_000003.11 (12625100..12705700, complement)	http://www.ncbi.nlm.nih.gov/gene/5894
<i>RANGRF</i>	17p13.1	NG_028189.1	NC_000017.11 (8288497..8290092)	https://www.ncbi.nlm.nih.gov/gene/29098
<i>RBM20</i>	10q25.2	NG_021177.1	NC_000010.11 (110641933..110839471)	https://www.ncbi.nlm.nih.gov/gene/282996

<i>RIT1</i>	1q22	NG_033885.1	NC_000001.11 (155897808..155911402, complement)	https://www.ncbi.nlm.nih.gov/gene/6016
<i>RPS6KA3</i>	Xp22.12	NG_007488.1	NC_000023.11 (20149911..20267514, complement)	https://www.ncbi.nlm.nih.gov/gene/6197
<i>RPS7</i>	2p25	NG_011744.1	NC_000002.11 (3622853..3628509)	http://www.ncbi.nlm.nih.gov/gene/6201
<i>RYR1</i>	19q13.2	NG_008866.1	NC_000019.10 (38433700..38587564)	https://www.ncbi.nlm.nih.gov/gene/6261
<i>RYR2</i>	1q43	NG_008799.2	NC_000001.10 (237205510..237997288)	http://www.ncbi.nlm.nih.gov/gene/6262
<i>SCN1B</i>	9q13.1	NG_013359.1	NC_000019.9 (35521555..35531353)	http://www.ncbi.nlm.nih.gov/gene/6324
<i>SCN3B</i>	11q23.3	NG_016283.1	NC_000011.9 (123499895..123525315, complement)	http://www.ncbi.nlm.nih.gov/gene/55800
<i>SCN4B</i>	11q23.3	NG_011710.1	NC_000011.9 (118004092..118023630, complement)	http://www.ncbi.nlm.nih.gov/gene/6330
<i>SCN5A</i>	3p21	NG_008934.1	NC_000003.11 (38589553..38691164, complement)	http://www.ncbi.nlm.nih.gov/gene/6331
<i>SCO2</i>	22q13.33	NG_016235.1	NC_000022.11 (50523568..50526439, complement)	https://www.ncbi.nlm.nih.gov/gene/9997
<i>SCRIB</i>	8q24.3	NG_030583.1	NC_000008.11 (143790920..143815379, complement)	https://www.ncbi.nlm.nih.gov/gene/23513
<i>SDHA</i>	5p15.33	NG_012339.1	NC_000005.10 (218223..264816)	https://www.ncbi.nlm.nih.gov/gene/6389
<i>SDHAF1</i>	19q13.12	NG_016869.1	NC_000019.10 (35995188..35996318)	https://www.ncbi.nlm.nih.gov/gene/644096
<i>SDHB</i>	1p36.13	NG_012340.1	NC_000001.11 (17018722..17054170, complement)	https://www.ncbi.nlm.nih.gov/gene/6390
<i>SDS</i>	12q24.13	NC_000012.12	NC_000012.12 (113392445..113403887, complement)	https://www.ncbi.nlm.nih.gov/gene/10993
<i>SGCD</i>	5q33-q34	NG_008693.2	NC_000005.9 (155462147..156194799)	http://www.ncbi.nlm.nih.gov/gene/6444
<i>SLC22A5</i>	5q31.1	NG_008982.2	NC_000005.10 (132369704..132395614)	https://www.ncbi.nlm.nih.gov/gene/6584
<i>SLC25A20</i>	3p21.31	NG_008171.1	NC_000003.12 (48856923..48898993, complement)	https://www.ncbi.nlm.nih.gov/gene/788
<i>SLC25A4</i>	4q35	NG_013001.1	NC_000004.11 (186064417..186071538)	http://www.ncbi.nlm.nih.gov/gene/291
<i>SLC25A4</i>	4q35.1	NG_013001.1	NC_000004.12 (185143263..185150384)	https://www.ncbi.nlm.nih.gov/gene/291
<i>SLC25A5</i>	Xq24	NG_013262.1	NC_000023.11 (119468400..119471396)	https://www.ncbi.nlm.nih.gov/gene/292
<i>SLC52A2</i>	8q24.3	NG_032872.1	NC_000008.11 (144358547..144361286)	https://www.ncbi.nlm.nih.gov/gene/79581
<i>SMAD3</i>	15q22.33	NG_011990.1	NC_000015.9 (67358036..67487533)	http://www.ncbi.nlm.nih.gov/gene/4088
<i>SMAD7</i>	18q21.1	NG_023330.1	NC_000018.10 (48919853..48950711, complement)	https://www.ncbi.nlm.nih.gov/gene/4092
<i>SMARCA4</i>	19p13.2	NG_011556.2	NC_000019.10 (10960922..11062282)	https://www.ncbi.nlm.nih.gov/gene/6597
<i>SNTA1</i>	20q11.2	NG_011622.1	NC_000020.10 (31995763..32031698, complement)	http://www.ncbi.nlm.nih.gov/gene/6640
<i>SOS1</i>	2p21	NG_007530.1	NC_000002.11 (39208690..39347686, complement)	http://www.ncbi.nlm.nih.gov/gene/6654
<i>SQSTM1</i>	5q35.3	NG_011342.1	NC_000005.10 (179806388..179838078)	https://www.ncbi.nlm.nih.gov/gene/8878
<i>STARD3</i>	17q11-q12		NC_000017.10 (37793333..37820454)	http://www.ncbi.nlm.nih.gov/gene/10948

<i>TAZ</i>	Xq28	NG_009634.1	NC_000023.10 (153639877..153650065)	http://www.ncbi.nlm.nih.gov/gene/6901
<i>TBX20</i>	7p14.2	NG_015805.1	NC_000007.14 (35199936..35254100, complement)	https://www.ncbi.nlm.nih.gov/gene/57057
<i>TBX5</i>	12q24.1	NG_007373.1	NC_000012.11 (114791735..114846247, complement)	http://www.ncbi.nlm.nih.gov/gene/6910
<i>TCAP</i>	17q12	NG_008892.1	NC_000017.11 (39665346..39666554)	https://www.ncbi.nlm.nih.gov/gene/8557
<i>TGFB3</i>	14q24.3	NG_011715.1	NC_000014.9 (75958061..75983011, complement)	https://www.ncbi.nlm.nih.gov/gene/7043
<i>TGFBR1</i>	9q22	NG_007461.1	NC_000009.11 (101867412..101916474)	http://www.ncbi.nlm.nih.gov/gene/7046
<i>TGFBR2</i>	3p22	NG_007490.1	NC_000003.11 (30647994..30735634)	http://www.ncbi.nlm.nih.gov/gene/7048
<i>TMEM43</i>	3p25.1	NG_008975.1	NC_000003.11 (14166440..14185180)	http://www.ncbi.nlm.nih.gov/gene/79188
<i>TMEM70</i>	8q21.11	NG_016618.1	NC_000008.11 (73976142..73982783)	https://www.ncbi.nlm.nih.gov/gene/54968
<i>TNNC1</i>	3p21.1	NG_008963.1	NC_000003.11 (52485107..52488057, complement)	http://www.ncbi.nlm.nih.gov/gene/7134
<i>TNNI3</i>	19q13.4	NG_007866.2	NC_000019.9 (55663135..55669100, complement)	http://www.ncbi.nlm.nih.gov/gene/7137
<i>TNNT2</i>	1q32	NG_007556.1	NC_000001.10 (201328136..201346836, complement)	http://www.ncbi.nlm.nih.gov/gene/7139
<i>TPM1</i>	15q22.1	NG_007557.1	NC_000015.9 (63334838..63364114)	http://www.ncbi.nlm.nih.gov/gene/7168
<i>TTN</i>	2q31.2	NG_011618.3	NC_000002.12 (178525989..178807423, complement)	https://www.ncbi.nlm.nih.gov/gene/7273
<i>TTR</i>	18q12.1	NG_009490.1	NC_000018.10 (31591767..31599024)	https://www.ncbi.nlm.nih.gov/gene/7276
<i>VANGL2</i>	1q23.2	NG_023420.1	NC_000001.11 (160400574..160428678)	https://www.ncbi.nlm.nih.gov/gene/57216
<i>VCL</i>	10q22.2	NG_008868.1	NC_000010.10 (75757836..75879918)	http://www.ncbi.nlm.nih.gov/gene/7414
<i>YAPI</i>	11q22.1	NG_029530.1	NC_000011.10 (102109957..102233423)	https://www.ncbi.nlm.nih.gov/gene/10413
<i>YWHAE</i>	17p13.3	NG_009233.1	NC_000017.11 (1344539..1400262, complement)	https://www.ncbi.nlm.nih.gov/gene/7531
<i>ZNF25</i>	10p11.21	NC_000010.11	NC_000010.11 (37949572..37976655, complement)	https://www.ncbi.nlm.nih.gov/gene/219749

Table S2. Silico predictive algorithms used in the study.

Category	Basis	Name	Website	Prediction Threshold
Missense prediction	Evolutionary conservation	SIFT	http://sift.jevl.org	<0.05 Deleterious >0.05 Tolerated
Missense prediction	Protein structure/function and evolutionary conservation	Align GVGD	http://agvgd.iarc.fr/agvgd_input.php	≥ C15 Probably Damaging
		Mutation Taster	http://www.mutationtaster.org	Disease causing
		Polyphen-2	http://genetics.bwh.harvard.edu/pph2	0.85 to 1 Probably Damage 0.15 to 0.85 Possibly Damage
Missense and insertion/deletions prediction	Contrasts annotations of fixed/nearly fixed derived alleles in humans with simulated variants	CADD	http://cadd.gs.washington.edu	≥ 20 1% most deleterious ≥ 30 0.1% most deleterious

Reference

1. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the association for molecular autopsy. Genet Med 2015;17:405–423.

Table S3. Variant identified in the patient

Gene	Protein	NM_004387.1	dbSNP	gnomAD	HGVD	SIFT	polyphen2	GVGD	Mutation Taster	CADD	Clin Var	ACMG classification
<i>NKX2-5</i>	p.Phe86fs	c.255_256delCT	n/a	n/a	n/a	n/a	n/a	n/a	n/a	28.7	n/a	PM2